TITLE PAGE

Title:
Multicentre Observational Study Describing the Systemic Response to Small-Area Burns in Children

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MANUSCRIPT

INTRODUCTION

Burns are a common injury in children less than five years of age worldwide. In high-, middle- and low-income countries, the predominant burn type is scalding by hot liquid, followed by contact and flame burns. [**1, 2, 4,**] The peak incidence of burn injuries in children in all countries is between 6 and 24 months of age, when children have become independently mobile but have not yet learnt hazard awareness and avoidance. In England and Wales, over 5,000 children under the age of five years are admitted to hospital for management of burn injuries each year.[1, 3] The majority (97%) of burn injuries sustained by children less than five years of age in the UK involve less than 10% of the Total Body Surface Area (TBSA).[5]

After their initial treatment, children with small-area burns may re-present to medical care with a febrile illness or isolated pyrexia. [6-10] Differential diagnoses include wound infection, systemic infection including Toxic Shock Syndrome (TSS) or bacterial or viral infection of non-burn origin. Definitive diagnosis of burn-related infection can only be made retrospectively using a combination of quantifiable microbiology testing, non-specific biomarkers of infection, recorded vital signs, and observed response to antibiotics.[11, 12] There is, therefore, a delay in obtaining a definitive diagnosis of infection of at least 48 hours.[13] This requires clinicians to prescribe antibiotics presumptively if infection is suspected. Another differential diagnosis is a normal physiological systemic inflammatory response to the burn injury in the absence of infection. [14, 15] In this situation, features of the paediatric Systemic Inflammatory Response Syndrome (SIRS) may be seen, but antibiotics are not indicated. The systemic response to burn injury is well documented in children with burns of more than 20% TBSA,[16-19] but there is little evidence describing the presence or magnitude of an inflammatory response in children with smaller injuries. In the last 10 years, there has only been one published article examining any aspect of the inflammatory response in children with burns of less than 10% TBSA. This study identified a rise in CRP during the first week post injury, but did not comment on clinical signs including temperature. [10]

Understanding the physiological response to small burn injury will assist clinicians in decision-making regarding the use of antibiotics in the management of children who re-present with a pyrexia after small area burn injury. The aim of this study was to describe the physiological response to burn injury in children under five years of age with burns of less than 10% TBSA. The limit of five years of age was chosen as this reflects the 'pre-school age child' and is the age limit most commonly referenced for epidemiological reports and guidelines for the diagnosis of pyrexia in young children [ADD refs Goldstein, NICE and WHO]. A burn size limit of 10% TBSA was chosen as, with only 3% of burn injuries in children under five years of age in England and Wales being greater than 10% TBSA, [Ref IBID] it is unlikely that we would be able to recruit sufficient patients with injuries of between 10 and 20% TBSA during the time period of the study to enable meaningful statistical analysis.

PATIENTS AND METHODS

Study Design and Patient Recruitment

A multicentre prospective observational cohort study, entitled 'Morbidity In Small Thermal Injury in Children' (MISTIC) was conducted between 13th January 2014 and 10th July 2015. NHS research ethics approval was granted for this study by NRES Committee South West – Exeter, England (13/SW/0306). The study followed a pre-specified protocol including a data analysis plan. Patients were recruited at three hospital sites in England: The South West Children's Burns Centre in Bristol, The St Andrew's Centre for Plastic Surgery and Burns in Chelmsford, and The Burn Centre at Birmingham Children's Hospital.

Children were eligible for inclusion in the study if they presented to the burn service within 48 hours of injury, were less than five years of age and had sustained a burn estimated to be less than 20% TBSA, from any cause and of any depth. The target population was children with burns of less than 10% TBSA, but children with an initial estimated burn size of up to 20% TBSA were included at the screening stage to avoid missing children whose burn size was over-estimated by referring services. Exclusion criteria included; any concurrent trauma, inhalation injury or if parents did not speak English and no translator was available.

Children were treated as an inpatient or outpatient depending on the severity and circumstances of the injury (e.g. safeguarding concerns or distance from home). Treatments undertaken were in line with the standard treatment at each recruiting sites and included the use of topical creams, non-adherent dressings, epidermal substitute dressings, surgical debridement +/- skin grafting, and analgesia as directed by the admitting clinical teams.

Objectives

1. To measure and describe changes in body temperature over the first seven days after burn injury.
2. To measure and describe changes in heart rate, respiratory rate, white blood cell count and serum C-Reactive Protein (CRP) levels over the first seven days after burn injury.
3. To investigate how any systemic inflammatory response (as indicated by elevated body temperature) is affected by burn size, burn depth, child age and sex.

Background Data

Details of patient age, sex and injury characteristics such as mechanism and severity of injury were recorded prospectively from the clinical case notes. The final TBSA and burn depth recorded by the burn surgeon were used in favour of any estimation given by a referring service. If the final burn size was deemed to be greater than or equal to 10% TBSA, the patient was withdrawn from the study.

Outcome Measures

Primary Outcome

The primary outcome measure was body temperature. All routine in-hospital temperature recordings (by nursing staff using an axillary thermometer) were recorded from the day of injury (day 0) up to seven days post injury (post-burn (PB) days 1 to 7). To enable the collection of temperature readings for children who were treated as outpatients, parents were provided with a thermometer (Omron Eco Temp Basic) and a temperature diary at recruitment into the study. Parents were given instructions to record their child's axillary temperature once a day for seven days. Parents were permitted to choose the time of day they took the reading, but it was requested that the reading be taken at the same time each day. When multiple temperature measurements were recorded for an individual child on a single day, the highest recorded measurement for that child on that day was used

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Secondary Outcomes

Secondary outcome measures were; heart rate (HR), respiratory rate (RR), white cell count (WCC) and serum C-reactive protein (CRP) level. All routine in-hospital measurements of these physiological observations and clinical investigations were recorded up to seven days post injury. Investigations were performed by each hospital's own laboratory. No additional measurements or tests were conducted for the sole purposes of this research.

Analyses

Statistical analyses were conducted using STATA v14 (StataCorp, 2015, Stata Statistical Software: Release 14). Both in-hospital clinical observations and parent-reported measurements of axillary temperature were combined for analysis. It was determined by the study group (JS, AY, IM and AE) that a child would need a minimum of five days of temperature recordings to be included in the analysis. This was to reduce the risk of outlying data points skewing results, whilst maximising the number of children that could be included in the analysis. A mean temperature was calculated for the cohort for each day post-burn. The change in cohort temperature over time was examined using a trend test with a value of $p<0.05$ accepted as showing a significant change in temperature over time. Temperature recordings were compared with the upper limit of normal for axillary temperature (37.3°C), and the threshold for the paediatric Systemic Inflammatory Response Syndrome (SIRS) criteria (38.5 ºC). [20, 21]

Sub-group analyses were performed to examine how temperature varied with patient and injury characteristics. We used the following groupings for these analyses:

- burn size (three burn size groups based on the British National Burn Care referral guidance;[22] <2% TBSA, ≥2 to <5% TBSA, and ≥5 to <10% TBSA),
- burn depth (any deep-dermal or full-thickness component to the injury),
- child sex (male or female),

- child age (using three age groups based on conventional physiological and epidemiological age cut offs: < 12 months, 12 to 24 months, and 24 months to five years).

The change in mean temperature over time for each group was assessed using the trend test, and differences between groups of patients with different demographic characteristics was assessed using a two-way analysis of variance (ANOVA) test.

The analyses of HR, RR, WCC and CRP included all recordings made from all children up to seven days post injury, regardless of how many readings they contributed. The variables were then analysed in the same manner as for temperature. Comparison of variable recordings was made with the accepted upper and lower limits of normal for each variable.[20, 23] The HR and RR recordings were split into two age groups to enable comparison with normal reference ranges; these age groups were: <12 months and ≥12 months of age.[24]

RESULTS

A total of 625 children were recruited into the study from the three sites (**Figure 1**). Data from all sites were pooled. Demographic details of the cohort are summarized in **Table 1**. The median age of children was 1.6 years and male children predominated 3:2. The majority of injuries were <2% TBSA in size and were superficial/partial thickness in depth. Too few children were recruited with flame, chemical, electrical, sunburn or friction abrasion injuries to conduct any meaningful analyses for these burn types and therefore these data were excluded from further analysis. The following results are therefore presented for patients with scald or contact burns only (patients combined, n=604).

Objective 1: Temperature over seven days after burn injury

Of the 604 children included, 369 (61%) had five or more days of temperature recordings and contributed a total of 1905 temperature recordings to the analysis (**Figure 1**). The overall trend was of a peak in temperature on day one post-injury followed by a fall in temperature over post-burn (PB) days four to seven ($p<0.001$). The mean temperature fell by 0.4 °C from PB days one to seven (**Figure 2**). The range of temperatures recorded on each day PB is shown in **Figure 3**.

The day with the greatest number of children with a temperature recording above the upper limit of normal for axillary temperature was PB day one. The days with the greatest number of children with a temperature recording above the threshold for paediatric SIRS criteria were PB days one, two and three (**Table 2**).

Objective 2: Effect of injury and patient characteristics on the temperature response

Burn size

Children with burns of <2% TBSA did not show any statistically significant variation in temperature over seven days post injury (**Figure 4a and supplementary material**). Children with burns of greater than 2% TBSA demonstrated a trend of higher temperatures for PB days one to three followed by a fall in mean temperature to PB day seven. Higher temperatures were seen in patients with burns of 5 to <10% TBSA, compared to children with burns of 2 to <5% TBSA ($p<0.001$). For children with burns of greater than 2% TBSA, the mean temperature experienced across the week increased by 0.1 °C for every 1% TBSA.

Burn depth

Children with a deep dermal or full thickness component to their injury recorded higher temperatures than those with purely partial thickness injuries ($p<0.001$) (**Figure 4b and supplementary material**).

Child age

Analysis by age revealed that children over 24 months of age did not show any significant variation in temperature over seven days post injury. Children under 24 months of age had elevated temperatures for PB days one to three followed by a fall across PB days four to seven (**Figure 4c and supplementary material**). When separated by year of age, the mean temperature experienced across the week for under one and one-year olds (36.7 and 36.8 respectively) was 0.4 °C higher than for two, three and four year olds (36.4, 36.4 and 36.5 respectively).

Child sex

Male children recorded higher temperatures than female children ($p<0.001$) (**Figure 4d and supplementary material**).

Objective 3: Secondary outcome measures

Fewer children had the secondary outcome measures recorded than had the primary outcome measure of temperature recorded, as the secondary outcome measures were only collected in hospital as part of clinical care. HR recordings were included from 238 children, RR from 223 children, and CRP and WCC measurements from 73 children.

HR and RR did not change over seven days for children <12 months of age (*not shown*), but for children ≥12 months of age both showed a rise to a peak on PB day three/four, followed by a return to baseline by PB day five. This trend was only significant for HR (HR $p<0.001$ and RR $p=0.062$ respectively) (**Figure 5a&b**). A day three peak was also seen in CRP level ($p=0.001$) (**Figure 5c**). No change in WCC was observed over seven days post injury ($p=0.421$) (**Figure 4d**).

DISCUSSION

The MISTIC study was designed to identify and describe the systemic inflammatory response to burn injury in children less than five years of age with burns of less than 10% TBSA, to assist in diagnosing the cause of pyrexia in this group and to identify children requiring additional treatment.

This study demonstrates a rise in body temperature following a burn, followed by a gradual fall from PB days two to seven. A rise in body temperature is a recognized feature of trauma, forming part of the systemic inflammatory response to injury. [25-27] In burns, tissue destruction secondary to a thermal insult at the site of injury initiates and perpetuates a local and systemic inflammatory response. In patients with burn injuries of greater than 20% TBSA, the systemic features of this response peak during the first week and decline over the next three to five weeks.[16-19, 25, 28-29] One of the main criteria of the systemic inflammatory response syndrome (SIRS) in children is a body temperature of >38.5°C [21]. The concept of SIRS in burn injury has been widely debated as it is considered to be a 'ubiquitous consequence of burn injury', though this statement is based on evidence derived from the study of only large burns (greater than 20% TBSA).[11] Studies that have included children with burns of greater than 10% but less than 20% TBSA have reported that the median time from injury to pyrexia >38°C was 16 hours and that body temperature begins to rise within six to 12 hours of injury and persists for at least 48 hours. [9, 30, 31] The MISTIC study included only children with burns of less than 10% TBSA and identified that the temperature peaked early on PB day one in children with burns of ≥2% TBSA.

Previous studies have identified a positive relationship between burn size and the magnitude of the inflammatory response and have hypothesized that this relationship is linear, but there is no previously published evidence that such a relationship exists in patients with burns of less than 20% TBSA.[15, 29, 32, 33] In the MISTIC study cohort, a positive linear relationship between burn size and the inflammatory response was reported with the mean temperature in the seven days following injury increased by 0.1°C with every 1% TBSA increase in children with burn size above 2% TBSA. Higher temperatures were seen in children less than 24 months old in the MISTIC study. Studies of children with larger burn injuries have found that a negative linear relationship is also seen between temperature and age.[9, 33-35] This could potentially be explained by the rapid onset, and shorter duration, of the stress response seen in younger children.[36] Male children demonstrated higher temperatures than female children in the MISTIC cohort. This is also seen in large burn and non-burn trauma, where females typically demonstrate an attenuated immune and inflammatory response in comparison to males.[37, 38] The variation of body temperature with patient and injury characteristics in this study supports the assumption that this temperature pattern is an indicator of a systemic inflammatory response.

In the MISTIC study heart rate and respiratory rate peaked on PB day three/four. This peak in heart rate may reflect a moderate metabolic 'flow' phase response to injury.[25, 31] Elevated heart and respiratory rates are also found concurrently with each other, and with elevated body temperature, regardless of the cause.[39] HR and RR can also be influenced by child distress or anxiety, which has not been adjusted for in this study.

CRP levels, but not WCC, also increased with a peak on day three. CRP increases within 4-6 hours of the onset of inflammation, peaks at around 36-50 hours, and has a half-life of 4-7 hours.[40] Increased CRP levels have been found from PB day two, peaking at around one week post injury, and correlating in magnitude and duration with burn size in children with burns <20% TBSA.[10, 41, 42] These findings are consistent with an inflammatory injury response.

This observational cohort study has some limitations. Simple statistical analyses were chosen to enable sub-group investigation of the data and to identify general trends in change in temperature and secondary variables over time. It is recognised that individual children contributed to temperatures on multiple days, and therefore greater precision in reporting of results may have been achieved with a mixed methods repeated measures model. However, there were insufficient patients in each group to enable this analysis to be performed whilst retaining sufficient power. Body temperature can be influenced by factors that have not been adjusted for in these analyses, including diurnal variation, use of antipyretic medication, environmental temperature and child activity. Clinical diagnostic and management decisions are made on the observed temperature and not on temperatures adjusted for these factors, and therefore the conclusions discussed here are applicable to normal clinical practice. Recordings of physical observations and clinical investigations were not available for all children in the recruited cohort and are therefore subject to selection bias. HR and RR were only recorded on children admitted as inpatients, which may have been for clinical or social reasons. Blood tests were only performed on those children who attended theatre or who became unwell and are therefore likely to reflect children with larger injuries and those children who may have experienced a post-burn illness. Despite this, the patterns of change in HR, RR, CRP and WCC are still informative, but should be interpreted on the understanding that they reflect a smaller patient group than the results presented for temperature. Use of differently calibrated devices and methods of measurement between hospital and home may have introduced measurement error, but the decision was made to record real behaviour to eliminate the potential effects of research (experimenter) bias.

Some of the children included in this cohort who experienced a post-burn pyrexia may have had a burn-related infection. A number of children in the cohort were started on antibiotics, but it was not possible to determine from the data set whether these were given as prophylaxis, started presumptively in response to pyrexia or prescribed following diagnosis of infection supported by microbiological evidence. Analyses of changes in variables in response to antibiotic use were therefore not performed. Further studies would be required, including quantifiable microbiology and validated point-of-care testing performed on all subjects at the time of elevated temperature, heart rate or CRP level, to accurately differentiate children experiencing a burn related infection from those simply experiencing an inflammatory response to injury, and to identify any physiological response to antibiotic use.

In spite of the above limitations, the results from this study demonstrate that consistent and predictable changes in temperature, HR, RR and CRP are observed in children less than five years of age following a burn of less than 10% TBSA. The rise in temperature, which is related to the size of the burn, is consistent with a systemic inflammatory response to burn injury that has been observed in children with larger burns.

CONCLUSION

The rise in body temperature early after burn injury that has been observed in children in this cohort supports the presence of a systemic inflammatory response in young children with small-area burns.

A young child presenting with an isolated raised temperature in the first two days following a small-area burn injury (<10% TBSA), who is otherwise well with no other symptoms or signs of infection, is likely to be experiencing an inflammatory response to their injury. These children may be managed with a period of observation without the need for early precautionary antibiotics. Children who demonstrate additional signs of infection, or who experience a raised temperature from post-burn day three onwards, with or without other symptoms or signs, may benefit from further investigation.

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REFERENCES

1. Reducing unintentional injuries in and around the home among children under five years. Public Health England; March 2018. PHE publications gateway number: 2017886.

2. 24th (Final) Report of the Home and Leisure Accident Surveillance System. Department of Trade and Industry; 2003. https://discovery.nationalarchives.gov.uk/details/r/C11522184 (accessed Sept 2019)

3. Brewster CT, Coyle B, Varma S. Trends in hospital admissions for burns in England, 1991-2010: a descriptive population-based study. *Burns* 2013;39(8):1526-34.

4. Kemp AM, Jones S, Lawson Z et al. Patterns of burns and scalds in children. *Arch Dis Child* 2014;99(4):316-21.

5. Dunn K. Data from the International Burn Injury Database (iBID), 2013 and 2019. Personal communication. http://www.ibidb.org/

6. Rodgers GL, Mortensen J, Fisher MC et al. Predictors of infectious complications after burn injuries in children. *Pediatr Infect Dis J* 2000;19(10):990-5.

7. Edwards-Jones V, Dawson MM, Childs C. A survey into toxic shock syndrome (TSS) in UK burns units. *Burns* 2000;26(4):323-33.

8. White MC, Thornton K, Young AE. Early diagnosis and treatment of toxic shock syndrome in paediatric burns. *Burns* 2005;31(2):193-7.

9. Childs C. Fever in burned children. *Burns Incl Therm Inj* 1988;14(1):1-6.

10. Steinvall I, Karlsson M, Elmasry M. C-reactive protein response patterns after antibiotic treatment among children with scalds. *Burns* 2018;44(3):718-723.

11. Greenhalgh DG, Saffle JR, Holmes JHt et al. American Burn Association consensus conference to define sepsis and infection in burns. *J Burn Care Res* 2007;28(6):776-90.

12. National Notifiable Diseases Surveillance System (NNDSS); Toxic shock syndrome (other than Streptococcal) (TSS) 2011 Case Definition. Centres for Disease Control and Prevention; 2011. https://wwwn.cdc.gov/nndss/conditions/toxic-shock-syndrome-other-than-streptococcal/case-definition/2011/ (accessed Sept 2019).

13. Poster J, Chu C, Weber JM et al. Specific Patterns of Postoperative Temperature Elevations Predict Blood Infection in Pediatric Burn Patients. *J Burn Care Res* 2019;40(2):220-227.

14. Schultz L, Walker SA, Elligsen M et al. Identification of predictors of early infection in acute burn patients. *Burns* 2013;39(7):1355-66.

15. Abdel-Hafez NM, Saleh Hassan Y, El-Metwally TH. A study on biomarkers, cytokines, and growth factors in children with burn injuries. *Ann Burns Fire Disasters* 2007;20(2):89-100.

16. Jeschke MG, Chinkes DL, Finnerty CC et al. Pathophysiologic response to severe burn injury. *Ann Surg* 2008;248(3):387-401.

17. Jeschke MG, Gauglitz GG, Kulp GA et al. Long-term persistance of the pathophysiologic response to severe burn injury. *PLoS ONE* 2011;6(7):e21245.

18. Gauglitz GG, Finnerty CC, Herndon DN et al. Modulation of the Hypermetabolic Response after Burn Injury. In: Herndon DN, editor. Total Burn Care. 4th ed: Elsevier; 2012. p. 355-60.

19. Sherwood ER, Traber DL. The Systemic Inflammatory Response Syndrome. In: Herndon DN, editor. Total Burn Care. 4th ed: Elsevier; 2012. p. 249-64.

20. Baxter C, Gorodzinsky F, Leduc D et al. Temperature measurement in paediatrics. *Paediatr Child Health* 2000;5(5):273-6+81-84.

21. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med* 2005;6(1):2-8.

22. National Network for Burn Care (NNBC): National Burn Care Referral Guidance. NHS Specialised Services; 2012. https://www.britishburnassociation.org/national-burn-care-referral-guidance/ (accessed Sept 2019).

23. Advanced Paediatric Life Support: The Practical Approach (5th Ed.). Samuels M, Wieteska S, editors. Manchester: Wiley-Blackwell, BMJ Books; 2011.

24. Kliegman R, Behrman RE, Nelson WE. Nelson textbook of pediatrics. Edition 20 / ed. Phialdelphia, PA: Elsevier; 2016. p. section 727.

25. Williams FN, Jeschke MG, Chinkes DL et al. Modulation of the hypermetabolic response to trauma: temperature, nutrition, and drugs. *J Am Coll Surg* 2009;208(4):489-502.

26. Mizushima Y, Ueno M, Idoguchi K et al. Fever in trauma patients: friend or foe? *Journal of Trauma-Inj Infec Crit Care* 2009;67(5):1062-5.

27. Schmitt BD. Fever in childhood. *Pediatrics* 1984;74(5 Pt 2):929-36.

28. Herndon DN, Tompkins RG. Support of the metabolic response to burn injury. *Lancet* 2004;363(9424):1895-902.

29. Caldwell FT, Jr., Wallace BH, Cone JB. The effect of wound management on the interaction of burn size, heat production, and rectal temperature. *J Burn Care Res* 1994;15(2):121-9.

30. Kim J, Rodgers LR, Long SS. 1998 Abstracts The American Pediatric Society and The Society for Pediatric Research. 864: Fever in Burned Children Usually is Not an Indication of Infection Nor Reason a Priori for Laboratory Investigation or Antibiotic Therapy. *Pediatr Res* 1998;43:149.

31. Childs C, Little RA. Acute changes in oxygen consumption and body temperature after burn injury. *Arch Dis Child* 1994;71(1):31-4.

32. Jeschke MG, Mlcak RP, Finnerty CC et al. Burn size determines the inflammatory and hypermetabolic response. *Crit Care* 2007;11(4):R90.

33. Dehne MG, Sablotzki A, Hoffmann A et al. Alterations of acute phase reaction and cytokine production in patients following severe burn injury. *Burns* 2002;28(6):535-42.

34. Jeschke MG, Norbury WB, Finnerty CC et al. Age differences in inflammatory and hypermetabolic postburn responses. *Pediatrics* 2008;121(3):497-507.

35. Childs C, Stoner HB, Little RA et al. A comparison of some thermoregulatory responses in healthy children and in children with burn injury. *Clinical science* 1989;77(4):425-30.

36. Kulp GA, Herndon DN, Lee JO et al. Extent and magnitude of catecholamine surge in pediatric burned patients. *Shock* 2010;33(4):369-74.

37. Jeschke MG, Mlcak RP, Finnerty CC et al. Gender differences in pediatric burn patients: does it make a difference? *Annals of surgery* 2008;248(1):126-36.

38. Angele MK, Schwacha MG, Ayala A et al. Effect of gender and sex hormones on immune responses following shock. *Shock* 2000;14(2):81-90.

39. Davies P, Maconochie I. The relationship between body temperature, heart rate and respiratory rate in children. *Emerg Med J* 2009;26(9):641-3.

40. Standage SW, Wong HR. Biomarkers for pediatric sepsis and septic shock. *Expert Rev Anti-Infe* 2011;9(1):71-9.

41. Jeschke MG, Finnerty CC, Kulp GA et al. Can we use C-reactive protein levels to predict severe infection or sepsis in severely burned patients? *Int J Burn Trauma* 2013;3(3):137-43.

42. Kraft R, Kulp GA, Herndon DN et al. Is there a difference in clinical outcomes, inflammation, and hypermetabolism between scald and flame burn? *Pediatr Crit Care Med* 2011;12(6):e275-81.